Complete Summary

GUIDELINE TITLE

Managing abnormal blood lipids. A collaborative approach.

BIBLIOGRAPHIC SOURCE(S)

Fletcher B, Berra K, Ades P, Braun LT, Burke LE, Durstine JL, Fair JM, Fletcher GF, Goff D, Hayman LL, Hiatt WR, Miller NH, Krauss R, Kris-Etherton P, Stone N, Wilterdink J, Winston M. Managing abnormal blood lipids: a collaborative approach. Circulation 2005 Nov 15;112(20):3184-209. [296 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

** REGULATORY ALERT **

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory information has been released.

On March 2, 2005, the U.S. Food and Drug Administration (FDA) issued a public health advisory describing revisions to the WARNINGS, DOSAGE AND ADMINISTRATION, CLINICAL PHARMACOLOGY, and PRECAUTIONS sections of the labeling for the drug Crestor (rosuvastatin calcium). The revisions include results from a Phase 4 pharmacokinetic study in Asian-Americans and highlight important information on the safe use of Crestor to reduce the risk for serious muscle toxicity (myopathy/rhabdomyolysis), especially at the highest approved dose of 40 mg. At this time, the FDA is also making statements about the muscle and kidney safety of Crestor based on extensive review of available information. See the FDA Web site for more information.

COMPLETE SUMMARY CONTENT

IDENTIFYING INFORMATION AND AVAILABILITY
DISCLAIMER

SCOPE

DISEASE/CONDITION(S)

- Dyslipidemia (abnormal blood lipids)
- Coronary artery disease
- Cerebrovascular disease
- Peripheral arterial disease

GUIDELINE CATEGORY

Evaluation
Management
Prevention
Screening
Treatment

CLINICAL SPECIALTY

Cardiology
Family Practice
Internal Medicine
Nutrition
Pediatrics

INTENDED USERS

Advanced Practice Nurses
Allied Health Personnel
Dietitians
Nurses
Physician Assistants
Physicians
Psychologists/Non-physician Behavioral Health Clinicians

GUIDELINE OBJECTIVE(S)

To review the complexities of lipid management throughout the lifespan and discuss the role and overall importance of a multidisciplinary and collaborative approach

TARGET POPULATION

Children and adults with dyslipidemia

INTERVENTIONS AND PRACTICES CONSIDERED

Assessment/Screening

1. Fasting lipid profile (including measurement of total cholesterol and low-density lipoprotein cholesterol (LDL-C), triglycerides (TGs), and high-density lipoprotein cholesterol (HDL-C)
2. Baseline creatine phosphokinase (CPK) (prior to initiation of statin therapy)
3. Assessment of treatment adherence

Prevention/Management/Treatment

1. Case management/collaborative clinical approach
2. Patient support and "patient connection" via mail, fax or internet
3. Lifestyle modifications
    - Weight control
    - Diet modification
    - Exercise program
    - Nutritional education
    - Smoking cessation
4. Pharmacological agents
    - Statins (rosuvastatin, atorvastatin, lovastatin, pravastatin, simvastatin, fluvastatin)
    - Bile acid-binding sequestrants (colestipol, cholestyramine, colesevelam)
    - Cholesterol-absorption inhibitors (ezetimibe)
    - Fibrates (fibrate or gemfibrozil)
    - Niacin
5. Dietary supplements (plant sterols/stanols and omega-3 fatty acids) (other supplements were considered but not recommended)

MAJOR OUTCOMES CONSIDERED

- Cardiovascular risk factor, cardiovascular and cerebrovascular morbidity and mortality rate
- Serum lipid levels
- Side effects of treatment
- Adherence to treatment program

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Not stated

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Review
Review of Published Meta-Analyses

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

This statement was approved by the American Heart Association (AHA) Science advisory and Coordinating Committee on July 26, 2005.

Expert peer review of AHA Scientific Statements is conducted at the AHA National Center. For more on AHA statements and guidelines development, visit http://www.americanheart.org/presenter.jhtml?identifier_3023366.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

A Collaborative Approach for Cardiovascular Health Promotion for Children and Youth: A Population and Public Health Perspective

Primary Prevention in Children

Both the National Cholesterol Education Program (NCEP) and the American Heart Association (AHA) emphasize the population approach as the principal means for primary prevention of coronary heart disease (CHD) beginning in childhood. By definition, population-based (public health) approaches are designed to shift the distribution of risk factors (i.e., blood cholesterol levels) of the target population to more desirable levels. Building on the NCEP recommendations, the AHA emphasizes lifestyle modification that includes "heart healthy" patterns of dietary intake and physical activity for the promotion of cardiovascular health and prevention of dyslipidemia and other risk factors for cardiovascular disease (CVD). The AHA dietary guidelines for children and youth were recently revised. For children 2 years old and older, emphasis is placed on the caloric and nutrient intake necessary for normal growth and developmental processes.

Current recommendations targeting primary prevention in children are noted in the table below titled "Primary Prevention in Children and Youth,". Given the prevalence for and trends in overweight and obesity in children and youth and the documented association between obesity and CVD risk factors, emphasis on increasing physical activity as part of weight management is an essential part of cardiovascular health promotion and risk reduction. The current AHA recommendations encourage pediatric healthcare providers to assess patterns of physical activity at every visit and to encourage physically active lifestyles for children and youth. Successful implementation of these recommendations (and the dietary recommendations) on a population level, however, will require major public health initiatives and the collaborative efforts of healthcare professionals, government agencies, schools, the food industry, and the media.

Primary Prevention in Children and Youth

Dietary modification

- Limit foods with
  - Saturated fats to <10% calories/day
  - Cholesterol to <300 mg/day
  - *Trans* fatty acids

Physical activity

- Increase moderate to rigorous ≥60 min/day
- Limit sedentary activities ≤2 hours/day

Identification of dyslipidemia

- Selective screening
  - Family history of coronary heart disease (CHD)
  - 1 parent with blood cholesterol ≥240 mg/dL
  - No parental history but CHD risk factors present
  - ≥1 of the following risk factors present: high blood pressure; smoking; sedentary lifestyle; obesity; alcohol intake; use of drugs or diseases associated with dyslipidemia

Identifying Dyslipidemia in Children and Youth

The NCEP and the AHA recommend an individualized/high risk approach to identifying dyslipidemia in children and youth (see table above). A fasting lipid profile allows for a comprehensive assessment that includes measurement of total cholesterol and low density lipoprotein cholesterol (LDL-C), triglycerides (TGs), and high-density lipoprotein cholesterol (HDL-C). The AHA recommends the averaged results of 3 fasting lipid profiles as the baseline for guiding treatment modalities.

The AHA endorses the guidelines established by the NCEP in setting the following definitions for acceptable, borderline, and high total cholesterol and LDL-C levels in children and adolescents between 2 and 19 years of age (see Table below entitled "Cholesterol Levels for 2- to 19-Year-Olds"). Although these cut points are recommended to guide treatment decisions, it is important to emphasize that no long-term longitudinal studies have been conducted to determine the absolute levels in childhood and adolescence that accelerate atherosclerotic processes and predict CHD in adult life.

Lifestyle modification with an emphasis on normalization of body weight and heart-healthy patterns of dietary intake and physical activity is the cornerstone of treatment for children and youth who are identified as having dyslipidemia. This approach should be supported through school-site education and heart-healthy programs as well as through community-based activities. In the pediatric office setting or in pediatric lipid clinics, the management of dyslipidemia is best accomplished via a multidisciplinary collaborative team approach. Nurses, nurse practitioners, and dietitians experienced in the treatment of dyslipidemia in children and youth are well positioned within these settings to facilitate lifestyle modification with children and families.

The AHA recommends an "adequate" trial (i.e., 6 to 12 months) of therapeutic lifestyle change before consideration of lipid-lowering medications. Three general classes of lipid-lowering agents are available and have been used in the treatment of dyslipidemia in children and adolescents. These include the bile acid sequestrants, niacin, and the Hydroxymethylglutaryl Coenzyme A (HMG-CoA) reductase inhibitors (statins).

Cholesterol Levels for 2- to 19-Year-Olds

Levels	Total Cholesterol, mg/dL	LDL-C, mg/dL
Acceptable	<170	<110

Levels	Total Cholesterol, mg/dL	LDL-C, mg/dL
Borderline	170-199	110-129
High	≥200	≥130

Collaborative Approaches to Primary and Secondary Prevention of CVD in Adults

Primary Prevention in Adults

Primary prevention of high blood cholesterol should be an important aspect of the societal approach to the promotion of cardiovascular health. Although cholesterol-lowering medications could be prescribed to people at high risk for developing high blood cholesterol, a long-term public health strategy that relies on providing medications to tens of millions of adults in the United States alone is not desirable for many reasons, including cost, inconvenience, and potential adverse effects. The approach of treating individuals at the highest risk, with selective attention to people with undesirable levels of blood cholesterol, could affect only the upper aspect of the cholesterol distribution, by reducing the cholesterol concentrations of only the people selected for individual treatment.

A growing body of evidence supports the promise of primary prevention of high blood cholesterol. Mean serum total cholesterol concentrations have declined in the United States during the past several decades.

Healthcare providers must support and advocate for continued public health approaches to improved nutrition, physical activity, and weight control.

Collaborative Approaches to Secondary Prevention and Treatment in Adults: The Effect of Case Management

The challenge to healthcare professionals is to implement programs that effectively identify those at highest risk and to offer cost-effective interventions. The case management model of care is an important intervention that meets this challenge. Case management provides systematic evaluation and implementation of medical treatments with regular follow-up of those at risk for a cardiac or vascular event.

Case management is a collaborative clinical model that uses expert evaluation, systematic intervention, and regular follow-up (see table below entitled "CHD Prevention in Adults: A Collaborative Approach"). Evidence suggests that case management results in an increase in short-term compliance, a reduction in emergency room visits, and a reduction in hospitalizations.

Patients perceive that they need individualized education and counseling, as well as skills to help them set goals and resolve difficulties with lifestyle changes. They respond well to a planned approach to accessing the medical care system appropriately. The ability to help them identify and sort out symptoms supports their overall health. Finally, case management systems also help patients and family members identify appropriate community resources.

The effectiveness of a collaborative approach through case management has been well documented during the last 2 decades both in the United States and globally. Case management has been shown to be an effective approach to the management of dyslipidemia and multiple risk factors in a number of populations. In addition, this approach to managing high-risk populations has shown improved outcomes as evidenced by a reduction in morbidity and mortality rates. Collaborative approaches that incorporate case management should be considered an ideal model for implementing multifactorial risk reduction (MFRR) in people with all forms of vascular disease such as peripheral arterial disease and cerebrovascular disease.

CHD Prevention in Adults: A Collaborative Approach

- Administered by nurses, health educators, and/or other healthcare providers
- Adherence to recommendations of national healthcare organizations (i.e., AHA, American College of Cardiology [ACC], National Institutes of Health [NIH])
- Open and regular communication with clinical experts and medical community
- Responsible for organization and collection of data for individual and clinical populations
- Success depends on attention to multiple tasks
    - Titration of medications
    - Management of side effects
    - Use of combination therapies
    - Use of lower-cost medications
    - Behavioral interventions for lifestyle modification

Nutritional Management of Lipids

The role of the nutritionist cannot be understated. Effective nutrition education and support can improve blood lipids and body weight through the intake of heart-healthy foods and caloric restriction; improve physical activity levels; reduce insulin resistance; improve the health of people with type 2 diabetes mellitus who control their glucose; and decrease the development of type 2 diabetes. The inclusion of nutrition is key to a collaborative approach.

Dietary management of LDL-C is a major goal of CHD risk management. In addition, drug-induced reductions in LDL-C result in a concurrent reduction in the rates of coronary disease morbidity and mortality. There is evidence from dietary studies that a marked reduction in LDL-C decreases the risk of CHD. Nutritional factors that affect LDL-C levels are noted in Table 5 of the original guideline document. The principal dietary strategy for lowering LDL-C levels is to replace cholesterol raising fatty acids (i.e., saturated and *trans* fatty acids) with dietary carbohydrate and/or unsaturated fatty acids.

AHA dietary recommendations for desirable lipid levels are noted in the table below.

AHA Dietary Recommendations for Achieving Desirable Blood Lipid Profile and Especially LDL-C

- Limit foods high in saturated fats
- Replace saturated fats with lower-fat foods
- Increase type of foods with unsaturated fat
- Carefully monitor intake of food high in cholesterol
- Severely limit foods containing *trans* fatty acids
- Increase foods rich in viscous fiber
- Increase foods containing stanol/sterol esters (special margarines, fortified orange juice, special cocoa/chocolate bars

Increasing viscous (soluble) fiber (10 to 25 g/day) and plant stanols/sterols (2 g/day) to enhance lowering of LDL-C is recommended. In addition, weight management and increased physical activity are recommended. An increase in viscous fiber of as little as 5 to 10 g/day is expected to reduce LDL-C by 3% to 5%. Inclusion of 2 g/day of plant stanols/sterols would be expected to reduce LDL-C by 6% to 15%. A 10-lb weight loss would be expected to decrease LDL-C by 5% to 8%. In conjunction with reductions in saturated fat and cholesterol, the inclusion of the above therapeutic diet options (including weight loss) is expected to decrease LDL-C by 20% to 30%. In addition to the therapeutic diet options of the therapeutic lifestyle change (TLC) diet, there is evidence that other dietary modifications, such as including soy protein and nuts, can lower LDL-C significantly.

Thus, the ratio of LDL-C or total cholesterol to HDL-C is one benchmark for estimating the risk of CHD.

The principal cardiovascular significance of an elevated TG level is that it is a component of the atherogenic dyslipidemia commonly found in patients with type 2 diabetes mellitus, metabolic syndrome, and excess adiposity. The triad of lipid abnormalities in these conditions consists of an elevated plasma TG level (>≈150 mg/dL), reduced HDL-C level (<40 mg/dL for men; <50 mg/dL for women), and a relative excess of small, dense LDL particles that accompanies total LDL-C levels that are generally normal. Adiposity is the principal nutrition-related influence that is found with atherogenic dyslipidemia, and Adult Treatment Panel III (ATP III) recommends that treatment be focused on reducing TG levels. Consequently, for these individuals, weight loss is a primary goal as a means to lower TG levels.

Among nutrients, the major determinant of elevated TGs in atherogenic dyslipidemia is dietary carbohydrate. In general, simple sugars and rapidly hydrolyzed starches have a greater glyceridemic effect than more complex carbohydrates and those consumed in conjunction with a higher intake of fiber. The recommended level of dietary fat is 25% to 35% of calories. Within this range, complex carbohydrates and a high-fiber diet are advised to facilitate TG lowering and to increase the levels of HDL-C and larger, more buoyant LDL particles. In addition, there is increasing evidence to support the beneficial influence of omega-3 fatty acids in the management of hypertriglyceridemia.

It is evident that a growing number of diet-based treatment options can be applied selectively to individualized diet therapy for both primary and secondary prevention of coronary disease. Healthcare providers are well positioned to markedly reduce CHD risk by diet as a result of this wide array of diet-based strategies that have an impact on multiple risk factors. This is best accomplished

by including the dietitian as a member of the collaborative team in the care of the patient with abnormal blood lipids.

Impact of Physical Activity on Blood Lipids and Lipoproteins

Physical activity beneficially influences most of the atherosclerotic risk factors. The impact of regular exercise on plasma lipids and lipoproteins has been clearly defined with regard to the interactions among lipids, lipoproteins, apolipoproteins (apo), lipoprotein enzymes, and the influence of various factors such as aging, body fat distribution, dietary composition, and cigarette smoking status.

The importance of physical activity, like nutrition, cannot be underestimated.

A collaborative approach to the care of adults with coronary risk factors through the use of nonphysician healthcare providers such as nutritionists, nurses, and exercise physiologists can help improve patients' success in the adoption of regular physical activity. Cardiac rehabilitation programs can offer assistance to healthcare providers with exercise education and supervision when indicated--another method of enhancing a collaborative approach to risk reduction.

The magnitude of change found for lipid and lipoprotein/lipid concentrations after a single exercise session is similar to that seen after the completion of a longitudinal exercise training program (see table 7 in the original guideline document). A measurable, beneficial effect on circulating lipids and lipoproteins/lipids may be expected after a single exercise session during which 350 kcal is expended, whereas trained individuals may require $\geq$800 kcal to elicit comparable changes. Lp(a) concentrations were not changed after short-duration exercise or longer-duration exercise sessions that required 1500 kcal of energy expenditure. To maintain beneficial lipid and lipoprotein/ lipid changes, exercise must be performed regularly.

Current data support a favorable impact for exercise training on lipid and lipoprotein profiles. Because much is known about the mechanisms responsible for changes in plasma lipid and lipoprotein modifications as a result of exercise training, a comprehensive medical management plan can be developed that optimizes pharmacological and lifestyle modifications.

With its favorable effect on many blood lipid abnormalities, physical activity/exercise training is a most appropriate intervention in a collaborative approach to the management of abnormal blood lipids. Activity should be undertaken at moderate to high intensity, 5 to 7 days/week, for at least 30 min/day and for $\geq$ 60 min/day by people who need to achieve weight loss. If this is done with an appropriate emphasis on nutrition and adherence, then body weight will likely be reduced and the need for medication therapy may be less in some people.

Including an assessment of an individual's physical activity patterns as part of every office visit will help to improve the recognition of its importance for both patient and provider. Developing a system for collaborating with healthcare providers who have expertise in behavior change, and exercise science for adults will support the important role of regular physical activity in regard to lipid management and overall risk reduction.

Drug Therapy

Medical therapies for dyslipidemia are key for people at high risk for the disease and for people with known atherosclerosis. A collaborative approach to medical therapies, often prescribed for a lifetime, has been shown to improve patient compliance and quality of life. Millions of Americans remain at risk from dyslipidemia, in spite of safe and effective treatments. Implementing a collaborative approach through the inclusion of nutritionists and nurses is key to long-term maintenance and safety of medical therapies.

Although effective drugs now exist to improve lipid profiles, no single drug is most appropriate under all circumstances. The 5 most common clinical situations in which drug therapy is needed are (1) elevated LDL-C; (2) elevated non-HDL-C in patients with high levels of TGs (200 to 500 mg/dL) despite attainment of LDL-C goals; (3) low HDL-C; (4) diabetic dyslipidemia; and (5) very high TGs and/or chylomicronemia syndrome. The appropriate treatment of these lipid abnormalities includes the use of the following classes of drugs: statins, resins, niacin, and fibrates, as well as fish oil, either singly or in combination.

An LDL-C goal of <100 mg/dL is considered optimum by ATP III. Newer guidelines were recently published addressing clinical options for further LDL-C lowering in high-risk and very high-risk patients. This report is based on compelling new evidence from clinical trials published after ATP III was released (see table below titled "New Features of ATP III").

Statins are the most potent agents for lowering LDL-C. These agents work by competitively inhibiting the rate-limiting step of cholesterol synthesis and upregulating LDL receptors in the liver. In order of potency, they are rosuvastatin, atorvastatin, simvastatin, and then, listed alphabetically, fluvastatin, lovastatin, and pravastatin.

Patients with markedly elevated LDL-C ($\geq$190 mg/dL) deserve consideration for drug therapy because they are likely to have either monogenic familial hypercholesterolemia, familial defective apoB-100, or polygenic hypercholesterolemia. The drugs of choice are statins. In patients with familial hypercholesterolemia, the inherited deficiency of LDL receptors and proportionate increases in LDL-C are countered by statin therapy. To potentiate the effects of statins, drugs that are active in the gastrointestinal tract can be added. These drugs include bile acid sequestrants and cholesterol absorption inhibitors.

Because major side effects of statins include myopathy, it appears reasonable to obtain a total creatine phosphokinase (CPK) level at baseline. Although this is not required, it may prove most useful if the patient develops muscle symptoms after starting a statin. If the baseline CPK is significantly elevated, then it is best to check for subclinical hypothyroidism or muscle disease before starting the statin. The other major side effect of statin use is liver toxicity, although the likelihood of liver transaminase elevations >3 times the upper limit of normal is small (in stable patients usually 1% or less). Liver transaminases (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) are obtained 6 to 12 weeks after statin therapy is initiated. Small increases in transaminases usually revert to lower values spontaneously and should not by themselves lead to the halting of statin therapy. If the ALT is $\geq$2 times the normal limit, then other

causes of a high ALT should be investigated, such as medication use, excessive alcohol use (a clinical clue is that AST is often greater than ALT when excessive alcohol use is present), or the presence of other conditions such as gallstones or a fatty liver (consider imaging the liver and gallbladder with ultrasound if the liver transaminase elevation is symptomatic). When ALT is >3 times the upper limit of normal and is confirmed on a repeat sample, statin therapy should be halted and an investigation should be undertaken to determine why this occurred.

A TG level $\geq$150 mg/dL is considered elevated. For patients with mildly elevated TG values (150 to 199 mg/dL), TLC may be adequate. Treatment of the disease states associated with high TGs, such as type 2 diabetes mellitus, chronic renal failure, nephritic syndrome, or hypothyroidism, may help reduce TG values toward normal. Drugs that elevate TGs, such as corticosteroid therapy, estrogen therapy, retinoid therapy, or high doses of beta-blockers, should be stopped or substitutions should be made. TG values vary greatly, so rather than suggest a "TG target," ATP III suggested the use of non-HDL-C as a surrogate for the total of atherogenic particles (all particles carrying cholesterol except for HDL).

Once LDL-C goals are reached, if TGs are $\geq$ 200 mg/dL, then non-HDL-C becomes a logical target for treatment. The goal levels for non-HDL-C are 30 mg/dL greater than the LDL-C goal. Statin therapy can be intensified in patients with elevated non-HDL-C. Nicotinic acid or fibric acid drugs (fibrates) are particularly useful for patients with combined elevations of cholesterol and TGs, low HDL-C, and raised non-HDL-C. For some high-risk patients, combination therapy with a statin and niacin or a statin and fibrate is required to achieve both LDL-C and non-HDL-C goals.

Low HDL-C (<40 mg/dL) is considered a tertiary goal in ATP III in patients with coronary disease who have reached their LDL-C and non-HDL-C goals. For all patients, behavioral changes that raise HDL-C can be recommended at the initial visit. These changes include losing excess weight, initiating regular exercise, stopping cigarette smoking, and avoiding excess carbohydrate calories in the form of sweetened foods and drinks. Because low HDL-C is a key component of the metabolic syndrome, reversal of a sedentary lifestyle and weight loss is likely to improve both HDL-C and the other parameters of this syndrome. For patients with isolated low HDL-C, HDL-C levels may not increase despite appropriate lifestyle change. Here, the goal is to lower LDL-C. For patients with CHD or CHD equivalents, drug therapy to improve HDL-C may indeed be appropriate once LDL-C and non-HDL-C goals are met. Evidence supporting medication therapy for abnormal blood lipids is noted in Table 9 of the original guideline document.

In patients with high TG plus chylomicronemia syndrome, prevention of acute pancreatitis is the primary goal. Three measures must be considered along with drug therapy if TGs are alarmingly high (>1000 mg/dL) and pancreatitis is a threat: (1) introduction of an extremely low-fat diet (15% of caloric intake); (2) removal of triggers such as high-fat meals and alcohol and drugs that greatly exacerbate hypertriglyceridemia such as oral estrogens (and tamoxifen), oral steroids, or retinoic acid; and (3) correction of disease states such as uncontrolled diabetes (this may indicate a need for insulin) and hypothyroidism. Fibrates can be effective medications for these patients.

Combination therapy with statins can be useful, but because there are few clinical trials to serve as guides, it is important to define the goals of therapy before adding another drug to statins. Thus, to lower LDL-C to attain goal levels, a gastrointestinal-active medication such as a bile acid–binding sequestrant (the resins cholestyramine and colestipol, or colesevelam, a nonabsorbable polymer) or a cholesterol-absorption inhibitor (e.g., ezetimibe) should be considered. Bile acid sequestrants are nonsystemic and hence ideal for young patients or good as a second drug in patients who are taking statins but are still short of their goal levels for LDL-C. These drugs have been shown to reduce coronary events in primary and secondary prevention trials. To raise low levels of HDL-C, niacin should be considered. Niacin raises blood glucose but has been shown to be effective in modifying lipid disorders in people with diabetes if glucose control is maintained. For a patient with high TG levels who has the metabolic syndrome or diabetes mellitus, a fibrate such as fenofibrate or gemfibrozil can also be considered. Caution should be exercised when combining fibrates with other cholesterol-lowering medications such as statins because of the risk of myopathy. Indeed, when a fibrate is combined with a statin, fenofibrate is the fibrate of choice because it does not affect statin glucuronidation, as is seen with gemfibrozil.

Bile acid sequestrants are safe drugs because they are nonabsorbable, but as expected, the major problems are gastrointestinal distress and constipation. Patients should be counseled to maintain water intake. A useful clinical tactic is to use half the dose of resin with psyllium. This helps reduce constipation while it magnifies the LDL-C-lowering effects of the resin. The older resins, cholestyramine and colestipol, are more prone to interfere with the absorption of other drugs such as thyroid medication, thiazide diuretics, or warfarin.

Ezetimibe is a cholesterol-absorption inhibitor. It is absorbed, undergoes glucuronidation in the liver, and localizes in the brush border of the intestinal cell. It lowers LDL-C by ≈ 20%, lowers TGs, and raises HDL-C slightly. Dosing studies show that it greatly augments LDL-C lowering when it is added to statin therapy. It also lowers plant sterol absorption from the gastrointestinal tract. The clinical benefits of this action are not known. It appears to be safe, although a rare hypersensitivity reaction with angioedema has been reported. The typical dose is 10 mg/day, and it can be taken at any time of the day.

Niacin has a unique side effect profile. Patients soon recognize the flushing and itching that comes from niacin ingestion. This is observed more strongly with unmodified niacin and is less of a problem with either the extended-release or the sustained-release forms. Because the flushing is prostaglandin mediated, an aspirin tablet taken ~1 to 2 hours before niacin ingestion can mitigate this side effect, which fortunately becomes less severe with time. All forms of niacin can raise blood sugar, uric acid, and liver enzymes and can cause upper gastrointestinal distress. Contraindications to niacin include liver disease, severe gout, and peptic ulcer disease.

The fibric acid drugs or fibrates have major actions on TGs because of their effects on the peroxisome proliferator activator receptor-alpha. When used in patients with lone hypercholesterolemia, LDL-C can be lowered as much as 22%; however, most often fibric acids will be used in patients with combined hyperlipidemia, as

seen in metabolic syndrome and diabetes. In these patients, LDL-C may actually rise slightly, TGs are lowered 20% to 50%, and HDL-C is raised 10% to 20%.

Medical therapies are complex and require patient education, systematic medical follow-up, and ongoing management. A collaborative approach among nursing, nutrition, and medicine will provide improved patient compliance, greater ability to reach lipid goals, and greater safety. A major benefit of a collaborative approach to medical therapies is the improved access that patients generally have when faced with questions and/or concerns such as those regarding side effects. Support and "patient connection" can be provided through mail, telephone, fax, and the Internet. These methods can save costs by reducing emergency department visits, unnecessary physician's office visits, and poor patient compliance.

New Features of ATP III

Focus on multiple risk factors

- Uses Framingham 10-year absolute CHD risk to identify patients for more intensive treatment (risk >20% in 10 years)
- Identifies people with multiple metabolic risk factors (metabolic syndrome) as candidates for intensified therapeutic lifestyle changes (TLC)

Identifies people with CHD equivalents

- Other forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, symptomatic carotid artery disease); diabetes; multiple risk factors that confer 10-year risk for CHD of >20%

Modifications of lipid and lipoprotein classification

- Identified LDL-C level <100 mg/dL as optimal
- Raised categorical low HDL-C from <35 to <40 mg/dL
- Lowered TG cut point (<150 mg/dL) to draw more attention to moderate elevations

Modifications of ATP III for LDL-C goals
TLC remains essential modality for LDL-C lowering

- *High risk* (CHD or CHD risk equivalents): LDL-C goal remains <100mg/dL with an optional goal <70 mg/dL
- *Moderately high risk* ($\geq$2 risk factors; 10% to 20% 10-year risk): LDL-C goal <130 mg/dL with optional goal of <100 mg/dL; at 100 to 129 mg/dL, consider drug options
- *Moderate risk* ($\geq$2 risk factors; 10-y risk <10%): LDL-C goal is <130 mg/dL; at $\geq$160 mg/dL, consider drug options
- *Lower risk* (0 to 1 risk factor): LDL-C goal is <160 mg/dL; at 160 to 189 mg/dL, consider drug options

Use of Supplements in the Management of Abnormal Blood Lipids: Do They Fit?

Current evidence suggests that omega-3 fatty acids are safe and may benefit patients with lipid disorders that include high TGs. For patients with high TG levels (>500 mg/dL), marine-derived omega-3 fatty acids at doses of 3 g/day have been shown to lower TGs by ≈ 30%. ATP III recommends that omega-3 fatty acids be used as an adjunct to pharmacological therapy for lowering TG. The AHA recommends 2 to 4 g/day of eicosapentaenoic acid plus docosahexaenoic acid for patients who need to lower their TG levels given under a physician's care. The most practical way to achieve this quantity of omega-3 fatty acids is through the use of fish oil supplements.

There are no available, well-tested supplements that achieve the magnitude of lipid lowering that is observed with traditional pharmaceutical therapies. With the exception of plant stanols and omega-3 fatty acids, most supplements have demonstrated only a small beneficial effect on blood lipids (see table below titled "Supplements and Functional Foods: Lipid Effects"). Thus, current data suggest a limited role for supplements in the treatment of abnormal blood lipids. Patient education regarding the benefits and risks of vitamins and supplements is an integral and important component in the treatment of dyslipidemia. Nutritionists are well positioned to provide information about supplements--an additional key reason for collaboration.

Supplements and Functional Foods: Lipid Effects

Supplement/Functional Foods	Mechanism	Lipid Lowering, Average % Change	Usefulness for Lipid Management
Vitamin E	Antioxidant	No significant change in TC/LDL; lowers HDL_2	May have harmful effect
Vitamin C, beta carotene	Antioxidant	No significant change in lipid profile	No clear benefit; may have harmful effect
n-3 Fatty acids (fish oils)	Inhibits VLDL synthesis	Lower TG 15% to 40%; dose 1 to 3 g/day	Useful adjunct for hypertriglyceridemia; may be useful in diabetes
Garlic	Unknown	Lowers TC/LDL ≈ 5%	No major role
Soy protein	May be phytoestrogen effect	Lowers TC/LDL ≈ 5% to 10%, nonsignificant increase in HDL; dose 25 g/day	Modest role; best used in place of high saturated fat foods
Plant sterols/stanols	Decreases dietary and biliary cholesterol absorption	Lower TC/LDL 9% to 20%, no change in HDL; dose 2 g/day	Moderate effect; may be useful adjunct

Fiber	Bile acid-binding action, decreases dietary cholesterol absorption	Lowers TC/LDL ≈ 5% to 15%; dose 25 to 30 g/day of dietary sources of fiber	Modest role; best used in place of high saturated fat foods

TC indicates total cholesterol

Adherence Issues

In no other arena is collaboration more important than when considering adherence. Behavioral science, social science, psychology, and medicine meet at this crossroads. Through collaborative efforts, adherence to important lifesaving interventions can be positively influenced.

Treatment of dyslipidemia may include a special eating plan, weight reduction, smoking cessation, regular exercise, and ≥ lipid-lowering medications. Although this therapeutic plan may represent the optimal treatment approach, it also highlights the challenge facing patients who are attempting to incorporate these changes into their lives (see table 11 of the original guideline document).

Patient-Related Factors: As with many patient-related factors, these situations call for an open dialogue between patient and provider that encourages the patient to examine the risks and benefits of the treatment with the guidance of the healthcare professional. The ability to maintain open communication with the patient will permit a discussion of many factors that may influence a patient's compliance and will go far in enhancing adherence.

Regimen-Related Factors: The regimen itself has a marked impact on the patient's adherence. A regimen that is consistent with the guidelines for treatment of dyslipidemia may be overwhelming to the patient and may need to be introduced in stages (e.g., start with dietary modification, then add other lifestyle changes, and finally, add pharmacotherapy). Depending on the patient's lipid values, the treatment components may need to be introduced in reverse order. If cost is a factor and the patient cannot afford lipid-lowering medication, then alternative strategies need to be tried, and dietary therapy should be emphasized. Even dietary therapy may need to be introduced gradually, with regular checkups to determine how the patient is progressing in implementing the dietary changes.

Provider-Related Factors: The provider plays an intricate role in the maintenance of adherence. Instructing physicians and nurses in educating and counseling patients and creating opportunities for them to practice their skills can increase their self-confidence in this area.

System-Related Factors: Numerous factors related to the system can markedly affect adherence. The system can enhance adherence; for example, it can provide a tracking system that facilitates charting a patient's lipids, weight, blood pressure, or medication refills, or it can provide numerous disincentives.

Well established, multidisciplinary systems designed to promote achievement of treatment goals by patients are in place. The collective efforts of the team can

address the multiple factors that influence nonadherence, can reinforce the message delivered by other members, and can increase the probability of success in achieving and maintaining treatment adherence.

Assessment of adherence must be incorporated into each clinical encounter. Accurate and affordable measures are lacking, however, and most have a bias toward overestimating adherence.

A variety of methods are available to measure adherence in the clinical setting (eg, biological and electronic measures, pill counts, pharmacy refill records, self-report).

Taking a nonjudgmental approach and giving patients permission to report that they are not following the regimen is essential for an open discussion. Acknowledge each time how difficult it is to take medications or make lifestyle changes. An explanation of how objective data such as weight or laboratory results relate to adherence can be included in the discussion. In follow-up sessions, always ask patients about adherence. Practical indicators of inadequate adherence may also include missed appointments and lack of response to incremental increases in dosage or treatment intensity. When adherence is less than adequate, interventions to improve adherence need to be considered.

Similar to how factors that have an impact on adherence are categorized, strategies to remediate poor adherence or enhance adequate adherence can be divided according to the factors that they address: the patient, the regimen, the provider, or the system. The use of a combination of strategies (e.g., behavioral counseling, educational approaches, supportive techniques) is recommended, as is targeting the multiple levels of adherence. Beginning with the patient, the provider needs to determine not only whether the patient is ready to make a change and is confident about implementing the treatment but also whether the patient has the knowledge, skills, and resources to start the plan. Given the patient's capabilities and resources, is the regimen appropriate for the patient? Is the provider able to work within the patient's restrictions and counsel the patient about what needs to be done? Finally, can the system assist the patient and provide services needed by the patient and the provider to enhance adherence? A number of intervention strategies are available to address adherence across the multiple levels from patient to the system of care delivery. These strategies are based on several theories and models of behavioral change (e.g., social cognitive theory, relapse prevention model, stages of change model) and have been tested in randomized, controlled clinical trials. Evidence supports their use in combination, in multiple settings, and by all members of the healthcare team.

To realize the benefits of current therapies, improved adherence to all components of a lipid-lowering therapy must be achieved. Many strategies may appear to be complex, time-consuming, and burdensome for the clinician to implement. A good start to addressing the problem of inadequate adherence would be to include the simplest of strategies (e.g., working with the patient to address common priorities, simplifying the regimen, asking the patient about adherence, reinforcing at each visit the importance of adherence) and build on these as resources permit. The use of adherence enhancing interventions has been shown to make a difference in the patient's clinical outcome.

Coronary Artery Disease

It is clear that a collaborative approach to administering lifestyle changes in conjunction with a systematic approach to the use of effective lipid-lowering medications will maximize the likelihood that patients will be treated to attain well-accepted risk factor goals and will minimize the likelihood of preventable coronary events. Extensive clinical trial data document the effects of pharmacological lipid-lowering therapy on clinical outcomes in patients with CHD.

Although the use of pharmacological agents in this setting is fairly straightforward, lipid-lowering drugs are costly, are frequently associated with side effects and compliance issues, and focus benefits only on lipid-related mechanisms of atherosclerosis. Maximization of nonpharmacological therapy for abnormal lipids, which includes modification of the quality of the diet, weight-loss interventions, and exercise programs, will serve not only to minimize dosage requirements for pharmacological lipid-lowering agents but also to provide substantial non-lipid-related preventive benefits.

The process of systematically initiating the use of lipid-lowering medications, along with aspirin, beta-blockers, and angiotensin-converting enzyme inhibitors, in patients hospitalized with an acute coronary event, in conjunction with dietary and exercise counseling, has been shown to benefit from a collaborative approach by healthcare professionals. In the Cardiac Hospitalization Atherosclerotic Management Program (CHAMP) program, an in-hospital, nurse-case manager approach resulted in increased use of these preventive medications and was associated with improved risk factor measures such as lower LDL-C levels and a reduction in recurrent MI and mortality at 1 year.

No single study has truly sorted out the relative value of combined nutritional interventions, exercise, and lipid-lowering drugs with regard to the lowering of coronary event rates, because their effects are overlapping and confounded by nonlipid effects of lifestyle changes that affect the atherosclerotic process. These include the effects of exercise, weight loss, and nutritional modification on factors such as insulin resistance, blood pressure, and indexes of inflammation. Collaboration provides the addition of expertise to improve lifestyle change and can synergistically improve the effects of medical therapies.

Cerebrovascular Disease

Despite the lack of a definitive association of elevated cholesterol with stroke risk, many guidelines include a recommendation for cholesterol monitoring and lowering of elevated levels because of the shared comorbidity of cerebrovascular disease and CHD.

Although the benefits of lipid-lowering therapies in stroke patients require further elucidation, it is important to remember that elevated lipid levels and cerebrovascular disease actually rarely occur in isolation. Comorbidity in terms of other vascular risk factors and other vascular disease is common, especially when considered over the lifetime of the patient. Just as the benefits of statins may not be limited to their lipid-lowering effects, the benefits of diet and exercise also have an effect on diabetes and hypertension and thereby reduce not only stroke risk but also the risk of coronary disease and peripheral vascular disease both in

stroke and other high-risk patients. Hence, a truly collaborative effort to reduce lipid levels in stroke patients is likely to have a benefit that extends beyond lipid lowering. Many physicians may assume that knowledge of healthy lifestyle choices and their impact on stroke risk are well known to patients; however, specific recommendations by physicians regarding exercise and diet do appear to influence patient behavior and should not be omitted.

Peripheral Arterial Disease

Peripheral arterial disease (PAD) is a major manifestation of systemic atherothrombosis that presents as occlusive disease in the arterial circulation to the lower extremities.

Numerous epidemiological studies have documented a 6-fold excess risk of cardiovascular mortality and a 3-fold excess risk of all-cause mortality. This risk is present even in patients who have not yet had a cardiovascular event, thus emphasizing the importance of early detection and aggressive treatment of this systemic disease. Given these data, the first treatment goal is to aggressively modify cardiovascular risk factors in patients with PAD and prescribe antiplatelet therapies. An aggressive risk-reduction strategy should lead to a reduction in overall risk of cardiovascular events. Primary evidence now supports the use of statins, angiotensin converting enzyme inhibitors, and clopidogrel in patients with PAD even without previous evidence of a cardiovascular event. Once these systemic goals have been accomplished, recognition of the daily limitations imposed by claudication and prescription of appropriate symptomatic treatments should become the next clinical priority.

Patients with PAD have a marked reduction in exercise performance, as evidenced by a reduction in peak oxygen uptake $\geq$50% when compared with age-matched healthy controls. Patients with claudication have a reduced walking speed and distance, have lower physical function scores on standardized questionnaires, have shorter 6-min walk distances and speeds, and even experience alterations in balance and coordination. Thus, an important treatment goal, as stated above, is to improve exercise performance, walking ability, and functional status.

For patients with PAD, a comprehensive approach to the management of lipid disorders involves exercise, nutrition, and medical expertise. A collaborative approach is more likely to improve patient quality of life as well as outcomes. Again, the focus must fall equally on medical therapies, surgical interventions, and prevention. Nutrition, physical activity, smoking cessation, stress management, and social support all play key roles in the care of people with complex illnesses such as peripheral vascular disease. Providing this care involves many collaborative partners with supportive medical systems.

Conclusion

This perspective on a collaborative approach to managing abnormal blood lipids presents an organized overview of the evidence that supports a multidisciplinary case-management approach to cardiovascular risk reduction and, particularly, abnormal blood lipids. The significance of incorporating a collaborative approach to cardiovascular risk reduction and ultimately improving cardiovascular morbidity and mortality is emphasized.

Primary prevention has demonstrated that population-wide influences on cholesterol levels shift the cholesterol distributions to lower levels and thus reduce the rate of increase of cholesterol concentration levels with aging. Behavioral and environmental influences specific to this reduction in cholesterol are best addressed by the collaboration of various healthcare professionals and public health efforts.

This collaborative approach goes beyond the traditional cardiovascular patient to address patients with PAD and cerebrovascular disease. Data support the assertion that aggressive lipid-lowering therapy in patients with peripheral vascular disease will improve cardiovascular morbidity and mortality rates and alleviate claudication symptoms. In addition, statin therapy has been shown to reduce the incidence of stroke in patients when lipid levels were reduced.

Ideal blood lipid levels can be accomplished only by adherence to lifestyle and pharmacological regimens. This is a complex process. It can be accomplished by addressing the multilevel components of potential barriers to adherence that are related to the patient, the regimen, the provider, and the system. By elevating the importance of adherence in the collaborative approach to the management of abnormal blood lipids, a more profound impact on the reduction of cardiovascular and cerebrovascular morbidity and mortality will be seen.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of evidence supporting the recommendations is not specifically stated.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate management of lipids in adults

POTENTIAL HARMS

Side effects of therapy

- Side effects of statin therapy include myopathy and liver toxicity.
- Bile acid sequestrants may cause gastrointestinal distress and constipation.
- Cholestyramine and colestipol may interfere with the absorption of other drugs such as thyroid medication, thiazide diuretics, or warfarin.
- Ezetimibe has been reported to be associated with a rare hypersensitivity reaction with angioedema.

- Niacin may cause flushing and itching, observed more strongly with unmodified niacin. All forms of niacin can raise blood sugar, uric acid, and liver enzymes and can cause upper gastrointestinal distress.

CONTRAINDICATIONS

CONTRAINDICATIONS

Contraindications to niacin include liver disease, severe gout, and peptic ulcer disease.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness
Staying Healthy

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Fletcher B, Berra K, Ades P, Braun LT, Burke LE, Durstine JL, Fair JM, Fletcher GF, Goff D, Hayman LL, Hiatt WR, Miller NH, Krauss R, Kris-Etherton P, Stone N, Wilterdink J, Winston M. Managing abnormal blood lipids: a collaborative approach. Circulation 2005 Nov 15;112(20):3184-209. [296 references] PubMed

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